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4-17892/-

Intravenous solutions for status epilepticus

Abstract

The invention relates to a pharmaceutical composition for intravenous administration of carbamazepine or oxcarbazepine. The pharmaceutical composition contains:

a) the active compounds carbamazepine or oxcarbazepine;

b) as solubiliser an etherified, water-soluble γ-cyclodextrin derivative;

c) the liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

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CONVENTION CASE.

COMPLETE SPECIFICATION

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INTRAVENOUS SOLUTIONS FOR STATUS EPILEPTICUS

APPLICATION NO. 4685/90
SPECIFICATION ... 21/12/90

CIBA-GEIGY AG, a body corporate organised according to the laws of Switzerland, of Klybeckstrasse 141, 4002 Basle, Switzerland

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Intravenous solutions for status epilepticus

The invention relates to pharmaceutical compositions for intravenous administration of carbamazepine, oxcarbazepine and metabolites of these compounds, dry products containing these compounds and a solubiliser, process for the preparation of the pharmaceutical compositions which can be administered intravenously and of the dry products, and the use of the pharmaceutical compositions in a therapeutic procedure, in particular as anticonvulsants for solutions for injection with a rapid onset of action for treating status epilepticus or for solutions for infusion.

Carbamazepine, 5H-dibenzo[b,f]azepine-5-carboxamide (Tegretol®, Tegretal®: Ciba-Geigy), is regarded as agent of first choice for the treatment of convulsions and states of severe pain. The commercial dosage forms are intended for oral administration, for example tablets containing 200 mg of active substance or syrups with a 2 % content of active compound.

Oxcarbazepine, 10,11-dihydro-10-oxo-5-dibenzo[b,f]acepine-5-carboxamide (sic) (Trileptal®: Ciba-Geigy) is likewise known as an anticonvulsant. Clinical findings on oxcarbazepine are described in several publications, for example in The Lancet, July 22, 1989, pages 196-198 or in Antiepileptic Drugs, Third Ed., Raven Press N.Y. 1989, Chapter 66, pages 913-924.

Because of the low solubility in water, see Intern. Clinical Psychopharmacology, Jan. 1990, Vol. 5, Supplement, pages 73-82, see page 74, Table 1, both products are suitable only for enteral dosage forms, for example tablets, capsules or syrups. Oral dosage forms of these types can be used prophylactically for regularly occurring administrations in order to ensure, under normal conditions of the patient without convulsions and with normal consciousness, a consistently high concentration of active compound in the blood.

The oral dosage forms with their relatively slow onset of action are unsuitable for acute epileptic attacks associated with life-threatening convulsive states, for example status epilepticus, where immediate administration with the fastest onset of action to terminate the convulsions are absolutely necessary. It is quite impossible to administer these dosage

forms, in contrast to intravenous solutions, during the fit. The same problem occurs with long-lasting states of intensifying pain.

Hence, for the onset of action within a short time which is absolutely necessary, there is a need for solutions for injection which are administered intravenously.

Solutions for infusion are required in hospitals in order to prevent the occurrence of epileptic attacks with convulsions in patients who are unconscious (pre- or post-operatively) or whose consciousness is diminished (quiescent periods during the treatment).

In particular, the incidents caused by sudden attacks during surgical interventions for patients at risk of epilepsy are especially dangerous.

However, a prerequisite for intravenous dosage forms (solutions for injection and infusion) is that therapeutically effective amounts of the active compound which is to be administered can be dissolved in water. Because of their low solubility in water, the minimum therapeutic dose of the two active compounds carbamazepine and oxcarbazepine can exist not in the dissolved state but only as suspension with solid particles, and the intravenous administration thereof is impermissible.

Various solubilisers are known for improving the solubility, for example hydrophilic cosolvents such as ethanol, glycerol, propylene glycol, liquid polyethylene glycols or lipophilic solubilisers such as lecithin, fatty acid polyglycol esters or fatty acid glycerol polyglycol esters. There are general problems associated with the use of such solubilisers because of poor tolerability, for example the risk of embolism, and lack of stability, for example demixing effects on storage of the parenteral solution.

The present invention is based on the object of preparing for the antiepileptics with low solubility in water, carbamazepine and oxcarbazepine, intravenous dosage forms which have a rapid onset of action, are well tolerated and have high stability and which can be used for the said epileptic attacks in patients at risk, in particular status epilepticus, either immediately after their occurrence or precautionally in the case of surgical interventions.

It has been found, surprisingly, that the solubility of carbamazepine and oxcarbazepine in water can be increased by using etherified γ-cyclodextrin derivatives, especially

hydroxypropyl-γ-cyclodextrin, and, at the same time, these active compounds can be dissolved or at least colloidally dispersed in water in a therapeutic amount suitable for intravenous administrations.

This surprising finding can be used to achieve the object on which the present invention is based. The invention accordingly relates to a pharmaceutical composition for intravenous administration of the compounds carbamazepine and oxcarbazepine which have antiepileptic activity and are sparingly soluble in water, containing:
a) the compounds carbamazepine or oxcarbazepine which have antiepileptic activity and are sparingly soluble in water, and metabolites thereof;
b) as solubiliser an etherified water-soluble γ-cyclodextrin derivative;
c) the liquid vehicle prepared for injection purposes and, where appropriate, other auxiliaries suitable for preparing intravenous presentations.

This pharmaceutical composition is distinguished by particular stability. Thus, no sedimentation, for example of active compound crystals and/or auxiliary particles, is observed in a period of up to several months. The composition is additionally suitable for the preparation of an intravenous dosage form containing a therapeutically effective dose of the relevant sparingly soluble antiepileptic both in a relatively small volume, for example 2-10 ml, of liquid vehicle and in large volumes of up to about 1.5 l for solutions for infusion.

The general definitions and terms used hereinbefore and hereinafter preferably have the following meanings within the scope of the description of the invention:

The term pharmaceutical composition comprises a mixture which can be administered and which consists of the active compound which is intended for administration and which is in a dose higher than the minimum therapeutic dose, of the liquid vehicle and of the auxiliaries suitable for the relevant dosage form, for example solution for injection or infusion, taking account of the mode of administration - in this case i.v.

The term intravenous administration defines the therapeutic measure of introducing a solution for injection or infusion of the relevant active compound into a vein of the patient and thus directly into the blood, the specific reason being an acute indication, in the present case convulsions consequent on epileptic brain activity, episodes or states of severe pain or the risk of convulsions during and after surgical interventions.

An example of a metabolite of carbamazepine and oxcarbazepine is 10-hydroxy-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide. This compound is detected as metabolite of oxcarbazepine and exists both as racemic mixture of its R and S enantiomers and in the form of its optically pure individual R and S enantiomers.

The term solubiliser defines an auxiliary or mixture of auxiliaries which increases the dispersibility of an active compound, or mixture of active compounds, which is sparingly soluble in water, to such an extent that therapeutically effective doses of the active compound or mixture of active compounds can be administered - in the present case i.v. - in dissolved or at least colloidal form. The term dispersibility defines a measure of the formation of true molecular solutions of the active compounds and of the auxiliaries in water as well as colloidal solutions, for example solutions of association colloids or molecular colloids, which are clear or opalescent and exhibit, where appropriate after filtration, especially with sterile filters with pore diameters of about 5-10 μm, no solid particles whatever, for example micellar solutions or spherocolloids, which can be separated only in the ultracentrifuge. The dispersibility can be indicated, for example, in mg or mmol of active compound per litre of water.

The ether groups of the etherified γ-cyclodextrin derivative are preferably defined as follows:

C_1-C_6Alkyl is preferably methyl or ethyl.

Carboxy-C_1-C_6alkyl is preferably carboxymethyl, it being possible for the carboxyl group to be in salt form, for example as sodium carboxylate group.

C_1-C_6Alkoxycarbonyl-C_1-C_6alkyl is preferably methoxy- or ethoxycarbonylmethyl.

Hydroxy-C_2-C_6alkyl in which the position of the hydroxyl group is higher than the 1-position of the C_2-C_4alkyl radical is, in particular, 2-hydroxyethyl or 2- or 3-hydroxypropyl.

γ-Cyclodextrin etherified by C_1-C_6alkyl, carboxy-C_1-C_6alkyl, C_1-C_6-alkoxycarbonyl-C_1-C_6alkyl and/or hydroxy-C_2-C_6alkyl, where the position of the hydroxyl group is higher than the 1-position of the C_2-C_4alkyl radical is, for example, a γ-cyclodextrin derivative

which has 8 anhydroglucose units and which is etherified on a primary hydroxyl group of the anhydroglucose unit by C_1-C_6alkyl, for example methyl or ethyl, as well as carboxy-alkyl, for example carboxymethyl or C_1-C_6alkoxycarbonyl-C_1-C_6alkyl, for example ethoxycarbonylmethyl, and on one to two secondary hydroxyl groups by hydroxy-C_2-C_4-alkyl, for example 2-hydroxyethyl or 2- or 3-hydroxypropyl, for example 2- or 3-hydroxy-propyl-methyl-γ-cyclodextrin or 2-hydroxyethyl-methyl-γ-cyclodextrin.

The γ-cyclodextrin derivatives substituted exclusively by hydroxy-C_2-C_4alkyl are preferred, for example 2-hydroxypropyl- or 3-hydroxypropyl-γ-cyclodextrin or 2-hydroxy-ethyl-γ-cyclodextrin.

γ-Cyclodextrin itself is a known cyclic compound with 8 anhydroglucose units (cycloocta-amylose). Each anhydroglucose unit is substituted in the 2-, 3- and 6-position by hydroxyl groups which can be etherified only partially and thus not completely. The degree of the substitution or etherification by C_1-C_4alkyl groups, C_1-C_6alkoxycarbonyl-C_1-C_6alkyl or carboxy-C_1-C_6alkyl groups is indicated by the characteristic number ADS = average degree of substitution. This characteristic number is an average value of the etherified hydroxyl groups per anhydroglucose unit. The ADS value of suitable derivatives is about 0.05 to 2.0, preferably about 0.2 to 1.5. The range from 0.5 to 1.2 is particularly preferred.

The degree of substitution or etherification by the said hydroxy-C_2-C_4alkyl groups is indicated by the characteristic number MDS = molar degree of substitution. This characteristic number indicates the number of moles of the second alkylating agent, for example propylene oxide or ethylene oxide, which have been used for the preparation of the etherified γ-cyclodextrin derivative. Because of the tendency to substitution of the formed hydroxyl group in the side-chain on possible further polymerisation and the increased use, caused by this, of alkylating agent, the MDS value may be higher than the ADS value. The MDS value of suitable derivatives is about 0.05 to 10, preferably about 0.2 to 2. The MDS value of about 0.25 to 1 is particularly preferred.

The preparation of the said γ-cyclodextrin derivatives is known or can be carried out in a manner known per se. Thus, γ-cyclodextrin derivatives which are substituted by C_1-C_4-alkyl and hydroxy-C_2-C_4alkyl can be prepared by reacting γ-cyclodextrin with at least one equivalent of alcoholate, for example sodium methanolate, in an aprotic solvent, for example dimethylformamide, acetonitrile or dimethoxyethane, and subsequently reacting with one to two equivalents of the second alkylating agent, for example ethylene oxide or

propylene oxide. The preparation of the C_1-C_6alkoxycarbonyl or carboxy-C_1-C_6alkyl derivatives is carried out in analogy to the etherification reactions known for cellulose ethers. The preparation of hydroxyethyl- or hydroxypropyl-γ-cyclodextrin is a one-stage procedure, reacting only with ethylene oxide or propylene oxide, for example by the process described in US Patent Specification 3,459,731 or in analogy to the method of J. Szejtli et al., Stärke 32, 165 (1980) or by the method of A.P. Croft and R.A. Bartsch, Tetrahedron 39, 1417 (1983).

Hydroxypropyl-γ-cyclodextrin derivatives with an MDS value of about 0.9, a water content of up to 7 % (weight loss after drying), a content of unsubstituted γ-cyclodextrin of up to 2 %, ash up to 0.1 %, propylene glycol residue up to 2.0 %, org. solvent residue up to 0.1 %, a minimum solubility in water of about 50 g/100 ml (25°) and a solubility in the organic solvents methanol, ethanol, dimethylformamide, dimethyl sulfoxide, pyridine, are particularly preferred.

Preferred hydroxypropyl-γ-cyclodextrin derivatives are those with the hydroxyl group in the 2- or 3-position of the hydroxypropyl radical and with an MDS value of about 0.25-1.0 and a mean molecular mass of 1300-1600.

These derivatives are commercially available, for example from the company Wacker or Consortium für Elektrochemische Industrie, D-8000 Munich.

The liquid vehicle prepared for injection purposes is a sterile, pyrogen-free aqueous solution which contains the active compound in a therapeutically effective dose, the solubiliser described hereinbefore and, where appropriate, other auxiliaries suitable for preparing solutions for injection.

Concerning the requirements "sterile" and "pyrogen-free" reference is made to the procedures which are published in national pharmacopoeias or the European pharmacopoeia and which require maximum organism counts of less than 10,000 organisms per litre in water for injection purposes. The establishment of the appropriate conditions corresponds to conventional pharmaceutical practice, for example electrodialysis or combination of reverse osmosis, ion exchange, active carbon filtration and sterilising filtration through membranes.

Examples of other auxiliaries suitable for preparing solutions for injection are water-

soluble ionic additives such as sodium chloride or glycine. In particular, the said water-soluble additives are contained in the prescribed amounts which are necessary for establishing isotonic conditions in the intravenous solutions. Also suitable for establishing isotonic conditions are water-soluble, physiologically inert compounds such as mannitol, glucose, sorbitol etc.

Other auxiliaries suitable for preparing injection solutions are, in addition, the known wetting agents or surfactants which can be used for liquid pharmaceutical formulations, in particular nonionic surfactants of the fatty acid polyhydroxyalcohol ester types such as sorbitan monolaurate, -oleate, -stearate or -palmitate, sorbitan tristearate or trioleate, polyoxyethylene adducts of fatty acid polyhydroxyalcohol esters such as polyoxyethylene sorbitan monolaurate, -oleate, -stearate, -palmitate, tristearate or trioleate or polyethylene glycol fatty acid esters such as polyoxyethyl stearate, polyethylene glycol 400 stearate or polyethylene glycol 2000 stearate, in particular ethylene oxide/propylene oxide block polymers of the Pluronic® (Wyandotte Chem. Corp.) or Synperonic® (ICI) type.

The said surfactants can be present in the intravenous formulation in ratios of amounts of active compound to surfactant from about 1:0.001 to 1:0.1, preferably from about 1:0.03 to 1:0.1, by weight.

The present invention preferably relates to a pharmaceutical composition containing
a) carbamazepine or oxcarbazepine;
b) as solubiliser γ-cyclodextrin etherified by C_1-C_6alkyl, carboxy-C_1-C_6alkyl, C_1-C_6alkoxycarbonyl-C_1-C_6alkyl and/or hydroxy-C_2-C_6alkyl, where the position of the hydroxyl group is higher than the 1-position of the C_2-C_4alkyl radical;
c) the liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

The present invention preferably relates to a pharmaceutical composition containing
a) carbamazepine or oxcarbazepine;
b) as solubiliser γ-cyclodextrin etherified by hydroxy-C_2-C_4alkyl, where the position of the hydroxyl group is higher than the 1-position of the C_2-C_4alkyl radical;
c) the liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

The invention particularly relates to a pharmaceutical composition containing

a) carbamazepine or oxcarbazepine;
b) as solubiliser hydroxypropyl-γ-cyclodextrin in which the hydroxyl group of the hydroxypropyl radical is located in the 2- or in the 3-position of this radical;
c) the aqueous liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

The invention additionally relates to the dry product consisting of the inclusion compound of carbamazepine or oxcarbazepine, of the etherified, water-soluble γ-cyclodextrin derivative and, where appropriate, water-soluble auxiliaries suitable for preparing dry products.

The preferred dry product consists of the inclusion compound of carbamazepine or oxcarbazepine in hydroxypropyl-γ-cyclodextrin, in which the hydroxyl group of the hydroxypropyl radical is located in the 2- or 3-position of this radical.

The invention likewise relates to a process for preparing a pharmaceutical composition for intravenous administration of the compounds carbamazepine and oxcarbazepine, which have antiepileptic activity and are sparingly soluble in water, which is characterised in that
α) an etherified, water-soluble γ-cyclodextrin derivative is dissolved as solubiliser in the liquid vehicle, carbamazepine, oxcarbazepine or a metabolite thereof and, where appropriate, other water-soluble pharmaceutical auxiliaries are added to the liquid vehicle and, where appropriate, the solution is homogenised; or
β) a dry product containing carbamazepine, oxcarbazepine or a metabolite thereof and the etherified, water-soluble γ-cyclodextrin derivative is prepared and, where appropriate, water-soluble auxiliaries suitable for preparing dry products are added and the dry product is dissolved in the liquid vehicle.

Process α
In this variant, pyrogen-free water which has been sterilised by filtration where appropriate is initially introduced and the solubiliser, especially the hydroxypropyl-γ-cyclodextrin, and the other auxiliaries are added, where appropriate with heating, for example in a temperature range from about 20° to about 100°C, preferably 40-60°C. The active compound, in particular ground, anhydrous carbamazepine, is subsequently added to this vehicle. The dissolving process can be speeded up or completed by final homogenisation, for example by treatment with ultrasound or high-speed stirring, for example with a high-speed stirrer from Vortex. The result is a clear solution which contains no aggregates

at all and is homogeneous. Thus, no light scattering of the nature of a Tyndall effect is observed.

The solution can be dispensed into ampoules or vials with volumes from about 1 ml to about 50 ml, depending on the content of active compound, which are then heat-sterilised (120°C/20 min) in an autoclave where appropriate, or it is sterilised by filtration and dispensed under aseptic conditions, for example into containers for solutions for infusion.

Process β

The dry product according to the invention is prepared by suspending, for example, the amount which is intended for the intravenous administration of active compound in micronised form in a suspending medium, for example pyrogen-free water which contains the solubiliser and, where appropriate, the pharmaceutically acceptable additives (auxiliaries), and removing the solvent.

The dry product can contain water-soluble additives or auxiliaries such as sodium chloride, mannitol or glucose, which are necessary, for example, for establishing isotonic conditions. After the additives have been dissolved in water for injection, the active compound is added and dissolved. Sterilisation by filtration can be followed by the preparation of the dry product by evaporation or by known freeze-drying methods, for example by dispensing a defined amount of the prepared suspension normally into suitable containers such as ampoules, for example glass puncture ampoules (vials), and freezing the puncture ampoules with contents at about -40° to -50°C and subsequently lyophilising under a pressure of about 0.2-0.6 mbar by slowly warming over a period of about 24-48 h to a final temperature of about 25°-35°C.

Surprisingly, it is possible with the said processes to prepare dry products, in particular lyophilisates, and from them reconstitutable solutions which are stable and suitable for injection.

The present invention likewise relates to the use of an etherified, water-soluble γ-cyclodextrin derivative for preparing an aqueous solution which can be administered intravenously, in accordance with one of the two process variants.

The present invention likewise relates to the use of the dry product which is obtainable by the said processes for preparing solutions for injection. These solutions for injection can

be administered intravenously.

The dry product obtainable according to the invention is preferably reconstituted immediately before administration as a clear solution in the intended amount of liquid, in particular sterile water for injection.

The homogeneous solution of the active compound is formed again by shaking up. In place of a dry product containing the active compound and all the other additives such as sodium chloride or mannitol, it is also possible to dissolve a dry product containing only the active compound and solubiliser b) - without additives c). This variant is suitable for preparing solutions for infusion.

The pharmaceutical compositions are distinguished by good storage stability. No deposition of precipitates or crystals from the solution is observed.

In a particularly preferred embodiment, solutions for injection, which contain the usual doses of 10-250 mg of active compound, are prepared with a total volume of 1.0-50 ml, in particular 2.0-10.0 ml.

These solutions can be used as ready-to-use products.

The dosage form according to the invention which can be administered intravenously has valuable pharmacological properties and can be used as antineuralgic and especially as anticonvulsant for the treatment of severe spastic states and convulsions, especially convulsions of the status epilepticus type and for the prophylactic protection of predisposed persons from such suddenly occurring convulsions in situations where the otherwise usual oral administration cannot take place, for example in cases of unconsciousness, paralyses, after accidents or during operations. The present invention likewise relates to the use of this presentation for the treatment of such diseases, especially of epilepsy.

The invention also relates in particular to the formulations and preparation processes described in the examples.

The examples which follow merely serve to illustrate the invention described hereinbefore; however, they are not intended to restrict the scope thereof in any way.

Example 1: To prepare a carbamazepine-containing solution for injection, 100.0 g of hydroxypropyl-γ-cyclodextrin (MDS = 0.6) are dissolved in 100 ml of pyrogen-free, double-distilled water. 1500 mg of carbamazepine are dissolved in 100 ml of this solution by stirring at room temperature (= 20°C). The solution is filtered, dispensed into ampoules each containing 10.0 ml and sterilised in an autoclave at 120°C for 20 minutes.
The solution has the following properties:

Content:	150 mg of carbamazepine in 10.0 ml
Appearance:	clear, colourless solution
pH:	6.5-7.0

Example 2: In a similar manner to Example 1, to prepare an oxcarbazepine-containing solution for injection, 100.0 g of hydroxypropyl-γ-cyclodextrin (MDS = 0.6) are dissolved in 100 ml of pyrogen-free, double-distilled water. 400.0 mg of finely ground oxcarbazepine are dissolved in 100 ml of this solution by stirring at 22°C. The solution is filtered, dispensed into ampoules each containing 10 ml, and sterilised in an autoclave at 120°C for 20 minutes.
The solution has the following properties:

Content:	40 mg of oxcarbazepine in 10.0 ml
Appearance:	clear, colourless solution
pH:	6.5-7.0

Example 3: To prepare serial dilutions for in vivo tests, the 50 % solution of hydroxypropyl-γ-cyclodextrin is diluted with water. The solubility at 22°C of oxcarbazepine in a 40 % aqueous solution of hydroxypropyl-γ-cyclodextrin is:

Content:	37 mg of oxcarbazepine in 10.0 ml
Appearance:	clear, colourless solution

This solution of oxcarbazepine in 40 % aqueous hydroxypropyl-γ-cyclodextrin is used for determining the anticonvulsant action.

Example 4: In a similar manner to Example 3, 1000 ml of a solution are prepared from 200.0 g of hydroxypropyl-γ-cyclodextrin (MDS = 0.6) and 1.59 g of oxcarbazepine in pyrogen-free, double-distilled water.

The solution has the following properties:

Content:	15.9 mg of oxcarbazepine in 10.0 ml
Appearance:	clear, colourless solution
pH:	6.5-7.0

Example 5: The acute protective action of carbamazepine and oxcarbazepine after intravenous administration compared with oral was determined by means of the maximum electroshock. The following methods were used:

Electroshock test on rats:
Tonic convulsions of the hind limbs were induced by administration of an alternating current of 50 Hz and 36 mA for 0.63 seconds using corneal electrodes. 10 rats were used per dose and unit of time; one group served as control. The number of rats which showed no tonic convulsions of the hind limbs was determined for each group. The ED_{50} was calculated using regression analysis by the method of Spearman and Kärber.

Electroshock test on mice:
Tonic convulsions of the hind limbs were induced by administration of an alternating current of 50 Hz and 18 mA for 0.2 seconds using corneal electrodes. 10 mice were used per dose and unit of time; one group served as control. The number of mice which showed no tonic convulsions of the hind limbs was determined for each group. The ED_{50} was calculated using regression analysis by the method of Spearman and Kärber. The volumes injected for i.v. administration are 5 ml/kg for mice and 1 ml/kg for rats.

Example 6: The pharmacological properties of the various solutions are shown in Tables 1 to 5. The anticonvulsant action of carbamazepine and oxcarbazepine occurs more rapidly after the intravenous than after the oral administration (Tables 4 and 5). Surprisingly, the ED_{50} are considerably lower after intravenous administration than after oral administration (Tables 4 and 5).

The ED_{50} of carbamazepine and oxcarbazepine for the protective action against the maximum electroshock in the rat are indicated in Table 1.

Table 1:

Substances	ED_{50} in mg/kg
Carbamazepine	2.5
Oxcarbazepine	3.44

The anticonvulsants were injected intravenously 15 minutes before the electroshocks. The ED_{50} values were calculated by regression analysis from three different doses (10 rats per dose).

The time-course of the protective action of carbamazepine after intravenous administration in rats is shown in Table 2.

Table 2:

Time in Minutes	Protection from the maximum electroshock ED_{50} in mg/kg
5	2.5
15	2.5
60	3.1

The ED_{50} values are calculated by regression analysis from three different doses (10 rats per dose).

Table 3 shows the time-course of the protective action of oxcarbazepine after intravenous administration to mice (ED_{50}).

Table 3:

Time in Minutes	Protection from the maximum electroshock ED_{50} in mg/kg
2.5	4.35
5	4.35
15	5.0
60	10.7
120	20% at 20 mg/kg

The ED_{50} values are calculated by regression analysis from three different doses (10 mice per dose).

Table 4 shows the comparison of the protective action of carbamazepine after intravenous and oral administration.

Table 4:

Time in Minutes	Protection from the maximum electroshock ED_{50} in mg/kg			
	intravenous		oral	
	Mice	Rats	Mice	Rats
2.5	3.24	3.0	10 % at 60 mg/kg	60.0
5.0	2.6	2.5	22.7	60.0
15.0	4.7	2.5	22.3	15.4
30	6.8	2.0	10.7	9.6
60	6.5	3.1	13.0	10.0
120	17.3	4.3	27.0	12.5

The ED_{50} values are calculated by regression analysis from three different doses (10 animals per dose). A suspension in Methocel® was used for oral administration of carbamazepine.

Table 5 shows the comparison of the protective action of oxcarbazepine after intravenous and oral administration.

Table 5:

Time in Minutes	Protection from the maximum electroshock ED_{50} in mg/kg			
	intravenous		oral	
	Mice	Rats	Mice	Rats
2.5	4.35	2.35	0 % at 30 mg/kg	60 % at 30 mg/kg
5.0	4.35	3.44	40.44	20 % at 30 mg/kg
15.0	5.0	3.44	14.48	12.18
30.0	7.07	3.44	15.74	12.18
60.0	10.72	4.85	17.77	15.85
120	20 % at 20 mg/kg	5.70	36.3	16.08

The ED_{50} values are calculated by regression analysis from three different doses (10 animals per dose). A suspension in Methocel® was used for oral administration of oxcarbazepine.

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Claims

1. A pharmaceutical composition for intravenous administration of the compounds carbamazepine and oxcarbazepine which have antiepileptic activity and are sparingly soluble in water, containing:
a) the compounds carbamazepine or oxcarbazepine which have antiepileptic activity and are sparingly soluble in water, and metabolites thereof;
b) as solubiliser an etherified water-soluble γ-cyclodextrin derivative;
c) the liquid vehicle prepared for injection purposes and, where appropriate, other auxiliaries suitable for preparing intravenous presentations.

2. A pharmaceutical composition according to claim 1 containing:
a) carbamazepine or oxcarbazepine;
b) as solubiliser γ-cyclodextrin etherified by C_1-C_6alkyl, carboxy-C_1-C_6alkyl, C_1-C_6alkoxycarbonyl-C_1-C_6alkyl and/or hydroxy-C_2-C_6alkyl, where the location of the hydroxyl group is higher than the 1-position of the C_2-C_4alkyl radical;
c) the liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

3. A pharmaceutical composition according to claim 1 containing:
a) carbamazepine or oxcarbazepine;
b) as solubiliser γ-cyclodextrin etherified by hydroxy-C_2-C_4alkyl, where the location of the hydroxyl group is higher than the 1-position of the C_2-C_4alkyl radical;
c) the liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

4. A pharmaceutical composition according to claim 1 containing:
a) carbamazepine or oxcarbazepine;
b) as solubiliser hydroxypropyl-γ-cyclodextrin in which the hydroxyl group of the hydroxypropyl radical is located in the 2- or in the 3-position of this radical;
c) the liquid vehicle and, where appropriate, other water-soluble pharmaceutical auxiliaries.

5. A dry product consisting of the inclusion compound of the compound carbamazepine or oxcarbazepine which has antiepileptic activity and is sparingly soluble in water, of the etherified, water-soluble γ-cyclodextrin derivative and, where appropriate, water-soluble

auxiliaries suitable for preparing dry products.

6. Dry product according to claim 5 consisting of the inclusion compound of carbamazepine or oxcarbazepine in hydroxypropyl-γ-cyclodextrin in which the location of the hydroxyl group in the hydroxypropyl radical is in the 2- or 3-position of this radical.

7. Process for preparing a pharmaceutical composition according to claim 1, characterised in that
α) an etherified, water-soluble γ-cyclodextrin derivative is dissolved as solubiliser in the liquid vehicle, carbamazepine, oxcarbazepine or a metabolite thereof and, where appropriate, other water-soluble pharmaceutical auxiliaries are added to the aqueous liquid vehicle and, where appropriate, the solution is homogenised; or
β) a dry product containing and the etherified, water-soluble γ-cyclodextrin derivative is prepared and, where appropriate, water-soluble auxiliaries suitable for preparing dry products are added and the dry product is dissolved in the liquid vehicle.

8. Use of an etherified, water-soluble γ-cyclodextrin derivative for preparing an aqueous solution of carbamazepine or oxcarbazepine which can be administered intravenously.

9. Stable intravenous solutions of carbamazepine or oxcarbazepine for use in a procedure for treating the human or animal body.

10. A pharmaceutical composition according to claim 1, substantially as hereinbefore described and exemplified.

11. A dry product according to claim 5, substantially as hereinbefore described.

12. A process for preparing a pharmaceutical composition according to claim 1, substantially as hereinbefore described and exemplified.

13. A pharmaceutical composition according to claim 1, whenever prepared by a process claimed in an preceding claim.

14. Use according to claim 8, substantially as hereinbefore described.

15. A stable intravenous solution according to claim 9, substantially as hereinbefore described.

IE 904685

Dated this the 21st day of December, 1990

F. R. KELLY & CO.

BY: _______________ EXECUTIVE

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AGENTS FOR THE APPLICANTS.